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(71)(72) Applicant and Inventor: AKBAROV, Abdurafik Bakhramovich [UZ/UZ]; ul. Tsvetochnaya, 27, Tashkent, 700053 (UZ).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ARIPKHODZHAEVA, Firuza Akhborovna [UZ/UZ]; Kara-Kamysh, 7-6-2/4, Tashkent, 700178 (UZ).

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(57) Abstract

The invention is related to the chemistry of coordination compounds, in particular, to the compound manganese with glutamic acid and vitamin C, producing medical effect in kidney disease treatment, possessing hypoglycaemic and diuretic effect, and also to the mode of its production. The purpose – creation of the compound intensively eliminating uremia toxines, restoring glomerular filtration in kidney diseases, intensively lowering the level of blood glucose in diabetes and showing expressed diuretic action. The new substance is more effective than the known ones. So, earlier reduction of the level of the uremia toxines in blood is reached, restoration of diuresis indices (including minute diuresis) and glomerular filtration is for the first time reached in treatment of kidney disease, fast and effective reduction of blood glucose at acute hyperglycaemia and at diabetes connected with pancreas disfunction. The substance is produced in water medium by interaction of 2 mol alkali with 1 mol glutamic acid, with the subsequenti njection of 1 mol salts manganese and 1 mol of vitamin C into reaction medium.

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COMPLEX COMPRISING THE COORDINATION COMPOUND MANGANESE, ITS MEDICAL EFFECTS AND THE MODE OF ITS PRODUCTION

The invention is related to the chemistry of the coordination compounds, in particular, to the coordination compound manganase with α - aminoacid and vitamin, which has medical effect in treating kidney disease and which possesses hypoglycaemic and diuretic effect and can be used in medicine.

The complex of trivalent cobalt with glutamic acid and methylmethioninesulphonium chloride – bis (monosubstituted glutaminat – O, N; O, O) methylmethioninesulphonium chloride – O, N cobalt(III) trihydratum [Akbarov A.B., Temirkhodjaev B.H., Complex of the cobalt (III) with glutaminic acid and methylmethioninsulphonia chloride, possessing antihepatitic and bloodcreating activity and method of its production// The preliminary patent. The description of the invention. UZ (11) 2332 B. 30.03.95. Bull. № 1]. This substance possesses antihepatitis and bloodcreating activity. But for this substance medical effect in kidhey disease treatment is not known as well as hypoglycaemic and diuretic effect.

The closest to the compound in technical structure and hypoglycaemic effect is bis-(+,– - methionine - picolenato) zinc tetrahydrate and mode of its production.

Bis (+, – - methionin - picolinate) zink is a coordination compound of zinc with two picolinate ions and two molecules of methionine – $C_{22}H_{30}N_4ZnO_8S_2 \cdot 4H_2O$. This substance possesses antidiabetic activity [Yunuskhodjzaaev A.N., Ergasheva M.J., Mukarramova U.A., Akramova G.S., Sadikova N.D. Bis - (+,– - methionin - picolinate) zink tetrahydrate, having antidiabetic activity // The preliminary patent, Description of the invention. UZ (11) 1801 B. 30.04.94. Bull. № 2].

The mode of production of the substance is interaction of zinc picolinate tetrahydrate with methionine in aqua medium. For synthesis of the compound the mixture of zinc picolinate tetrahydrate and methionine is suspended in small amounts of water, while stirring during 1 hour. The final product is precipitated by acetone separated and washed by acetone and ether.

For this substance the medical effect in kidney disease treatment and diuretic effect is not known.

Next preparation is lespenephril, used for reducing azotemia (nitratemia) in cases of renal failure, acute and chronic nephritis, following by hyperazotemia (hypernitratemia).

The preparation is a sum of biologically active substances (catehine and flavones)

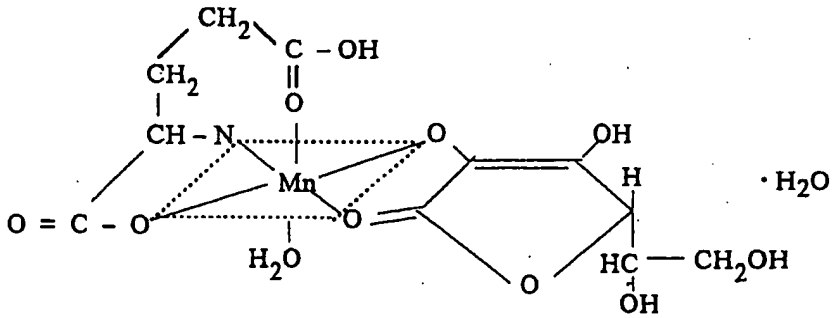
isolated from Lespedeza capitata. The result of using the preparation is increasing of diuresis and excretory of nitro- compound with urine [Mashkovskiy M.D. Medicinal means (Manual on pharmatherapy for the doctors). Tashkent: Medicina, 1987. V.1. P.500]. Lespenefril is administered orally and as injection. The preparation is administered (as 70 % alcoholic solution) 1 - 2 tea spoonful a day, and in more complicated cases – 2 - 3 (up to 6) teaspoonful a day. The preparation as injection is administered on the average 4 times a day in cases of renal failure, and 5 -10 vials a day during 10 days in more complicated cases.

The drawbacks of lespenephril are long term treatment and multiple injections. The application of the preparation inwards requires long time for displaying clinical effect, as lespenephril is administered in several 2 - 3 week courses. When Lespenephril is taken glomerular filtration, minute diuresis are not increased. Moreover hypoglycaemic effect is not known for the preparation.

The purpose of the invention is creation of the complex compound on the basis of manganase, α- amino acid and vitamin, having simultaneously medical effect in kidney disease and diabetes treatment, showing the diuretic effect, showing clinical effect in short time of application, and development of the mode of its production.

The purpose is achieved by receiving the coordination compound manganase with glutamic acid and vitamin C (γ–lacton–2,3–dihidro–L–gulonic acid) having the structure $C_{11}H_{15}MnO_{10}N \cdot 2H_2O$, having medical effect in kidney disease, hypoglycaemic and diuretic effect.

The offered substance has the following structure according to IR spectroscopy and DTA:



The carbonyl group $CH_2(\gamma)$ - COOH(δ) of the fragment of an ion glutamic acid can also contact to metal - ion of the next molecule of a complex, thus displaying bridge nature of coordination.

The purpose is achieved also because in the process of production of the coordination compound manganase with glutamic acid and vitamin C , bi substituted salt of glutamic acid interacts with salt manganase, with subsequent injection of vitamin C

into the reaction medium. Thus all components interact at equimolar ratio.

The received complex manganase with glutamic acid and vitamin C has high medical effect in kidney disease treating, it displays obvious hypoglycaemic and diuretic effect (tabl. 1 - 8). And, its specific activity is displayed in rather short interval of time.

Received coordination compound manganase with glutamic acid and vitamin C is the powder of gray – yellow colour, well dissoluble in water, non dissoluble in solution of acetone or ether. Melting temperature of previously dried up substance at 60° C during two hours makes 124 - 127° C.

Data of the elementary analysis of the coordination compound:.

Is found, in % : Mn - 13.40; N - 3.75; H_2O - 8.92.

For $C_{11}H_{15}MnO_{10}N \cdot 2H_2O$ calculated, in %: Mn - 13.33; N - 3.40; H_2O - 8.74.

When the substance is isolated by the method of sublimation drying, the amount of molecules of water, depending on selection of a temperature mode and vacuum depth can vary from one to three.

In a IR - spectrum of the coordination compound the following basic strips of absorption ($\pm$ 2 sm^{-1}) δ(O - H) $\approx$ 1370; ν_s(OCO) = 1409; ν_{as}(OCO) + ν(C=C) = 1595 (wide), ν (C=O) = 1723; $\nu(NH_2)$ = 3370 - 3212 (wide) are observed.

In a heating curve DTA of the coordination compound endotermic effects with maxima at 100, 155 and 185° C and exotermic effects with maxima at 245 and 475° C are observed. The first endoeffect indicates removal of one molecule of water. On a curve TG the loss of weight makes 4.45 % , in case of removal of one molecule of water loss of weight makes up theoretically 4.37 %. The second effect is connected with separation of the second molecule of water. Thus, the loss of weight on a curve Tr makes 4.47 %, culculated 4.57 %. These effects indicate presence of various in a nature molecules of water, one intrasphere (endotermic effect at 155°C), and one intersphere (endotermic effect at 100° C) molecules.The third endotermic effect is the consequence of the intensive decomposition of the organic part of the complex. Exotermic effects at 245 and 475° C are caused by decomposition and burning of the products of disintegration of the complex.

The description of the mode of production of the compound.

Example 1. To the water solution of 2 mol natrium or potassium hydroxide add 1 mol of glutamic acid and mix up to dissolution of the latter. To a received cooled solution of bi substituted salt of glutamic acid add the water solution of 2 mol chloride or manganase acetate or any other water-soluble salt manganase. Reaction medium is mixed during one hour. Thus some precipitation drops out. The precipitation is separated and

cleared of an impurity (natrium or potassium salts of inorganic nature). The cleared and dried up product is added to the water solution of vitamin C and is mixed during two hours. As a result the components should react at equimolar ratio. The proposed substance is isolated from the solution being precipitated by spirit, or acetone, or the method of sublimation drying.The output is no less than 88,6 %.

Example 2. To the water solution of 2 mol natrium or potassium hydroxide add 1 mol of glutamic acid and mix up to dissolution of the latter. To the received cooled solution of bi substituted salt of glutamic acid add the water solution of 1 mol of manganase of chloride or manganase acetate or other water-soluble salt manganase. Reaction medium is being mixed during one hour. As a result precipitation drops out. To the reaction medium add 1 mol of vitamin C and continue to mix it during 2 hours. Thus a transparent solution will be formed. The target product is precipitated from mother solution of ethanol or acetone and is cleared of an impurity (natrium or potassium of salts unorganic nature) by the method of repeated recristallization. The output - 81.2 %.

The research of indices of acute toxicity of the substance at its parenteral injection was conducted on white mice of both gender with weight of a body 18 - 23 g. The substance injected unitary, intravenously in doses 40 ÷ 100 mg/kg. Received were data processed statistically by the method of Litchfield and Wilcockson and updated by Rote. Thus was established, that Lethal dose (LD_{50}) indices for the offered substance makes 60.0 (55.3 ÷ 65.7) mg/kg at P = 0.05.

The acute toxicity index of the substance was also studied at its unitary oral injection. The substance was infused into the animals as water solution with the probe with increasing dose. During the experiment maximum amount of the infused preparation made 600 mg/kg. However, even at such a high dose fatal cases in the group of experimental animals were not observed.

To observe medical effect of the substance in kidney diseases on white rats the model of acute renal failure was reproduced.

In the experiment were used white male - rats with the weight of body 162 - 185g. Acute renal failure was reproduced by intramuscular injection of 50 % water solution of glycerine in a dose 10 mg/kg.

The animals were divided into two groups: experimental and control. The animal of the experimental group on the expiration of 24 hours from the beginning of the experiment during 10 days were injected the offered substance in a dose 10 mg/kg intravenously. The animals of the control group during ten days received parenteral water for injections in the same volumes, as animals of the experimental group

For the estimation of the functional condition of kidneys and efficiency of the

substance biochemical research methods were used.

On the expiration of 24 hours after injection of glycerine in the experimental animals the control test of urine and blood was carried out Thus was identified, that after the glycerine injection albumen in urine and, hypernitratemia in blood appeared, which is typical for acute renal failures. Acute renal failure was accompanied also by essential reduction of impellent activity and daily diuresis indices (tabl.1).

The conducted researches have shown, that for the tenth day of the treatment by the substance general condition of the animals and the indices of the biochemical test did not practically differ from indices of the intact animals. At the same time in the group of the control animals constraint was observed, the biochemical test of their blood much differed from indices of the intact animals (tabl.1)

It is necessary to note, that the substance produces essential effect on the process of reduction of daily volume of diuresis of the animals with acute renal failure already on the expiration of 24 hours from the initial injection. So, for example, at reproduction of acute renal failure, daily diuresis of the animals was reduced twice concerning indices of the intact animals. In the group of the animals receiving substance the essential increase of daily diuresis indices was observed already after the first injection. The upward tendency of the level of daily diuresis was maintained and in the consequent days of the experiment. So, for example, on the 10 day of the experiment diuresis index was higher than the average daily index of the intact animals. And, this index 2.5 times exceeded the index of diuresis of the animals with acute renal failure, 1.5 time exceeded the index of diuresis of the animals of the control group for the same period of research (tabl.1).

Table 1

Influence of the compound in dose 10 mg/kg on urination and biochemical bloodidices in acute renal failures

Studied indices	Index of the intact animals	Animal groups and observation periods					
		Control group of animals			Experimental group of animals		
		in 24 hours	in 5 days	in 10 days	in 24 hours	in 5 days	in 10 days
Volume of excreted urina, ml/day	4.21 ± 0.59	2.43 ± 0.70	3.10 ± 0.32	4.16 ± 0.47	5.23 ± 0.78	6.05 ± 1.28	6.65 ± 1.28
Ammonia, mmol/l	17.9 ± 1,34	41.6 ± 1.58	42.72 ± 1.63	39.61 ± 1.09	37.90 ± 1.22	29.6 ± 1.51	16.3 ± 0.52
Urea, mmol/l	5.9 ± 0.44	12.46 ± 0.69	12.72 ± 0.82	13.14 ± 1.09	11.90 ± 0.89	8.75 ± 0.51	7.30 ± 0.52
Creatinine, mkmol/l	87.4 ± 1.79	191.62 ± 3.76	190.59 ± 4.86	188.60 ± 6.03	189.50 ± 3.32	100.07 ± 2.12	92.50 ± 1.50
Minute diuresis, ml/min ($\times 10^{-3}$)	2.86 ±0,14	1.68 ± 0.12	2.15 ± 0.13	2.88 ± 0.15	3.63 ± 0.12	4.20 ± 0.11	4.62 ± 0.14

The substance has high medical effect and in chronic glomeronephrite treating. The medical effect of the substance is displayed not only in normalization of biochemical indices, but what is also important, under its influence in 10 days minute diuresis is completely restored and glomerular filtration index (tabl.2) is practically normalized.On the basis of the received data it is possible to conclude, that the offered substance produces high effect in kidney disease, which is expressed in restoration of kidney excretory function and in normalization of biochemical indices of blood.

Ihe influence of the substance in experimental hyperglycaemia, caused by hypertonic glucose solution or alloxane was studied on male rats with weight of a body 170 - 200g.

Experimental acute hyperglycaemia was induced in 72 rats by intraperitoneal injection hypertonic(20 %) glucose solution in a dose 5g on kg of weight of the animal. The blood for the test was taken from the end of the tail prior to the beginning of the experiment and by decapitation every 30 min. during 2 hours after intravenousinjection of the substance. During the experiment the influence of the two doses (5 and 10 mg/kg) of the substance parenterally injected on hyperglycaemic background was studied. The animals of the control group were injected with saline solutions in the appropriate volumes.

The blood glucose level was defined by the ortotoluidic method. The results of the conducted researches have shown, that blood glucose level of the animals of the control group remained authentically high during the first 90 minutes. It was clearly seen in 60 minutes since the initial glucose injection . By that time the level of blood glucose exceeded the intact animals index by 37.7% (tabl.3).

After injection of the substance in a dose 5 mg/kg significant reduction of blood glucose was observed. In particular, in 30 minutes after unitary injection of the preparation the glucose level did not practically differ from the index of the intact animals. The normalization of blood glucose level was maintained in the subsequent periods of observation (tabl. 3).

Hypoglycaemic effect of the preparation at a dose 10 mg/kg was more obvious than the effect observed at minimum therapeutic dose.

On the basis of the analysis of the received data it is possible to conclude, that hypoglycaemic effect of the preparation, at unitary parenteral injection is displayed at minimum, and at optimum therapeutic doses.

The received data show, that the offered substance has good glucose reducing effect at acute hyperglycaemia after its unitary injection.

Table 2

Influence of the Lespenefhril and the offered substance on the biochemical blood and urine indices and on the excretory kidney function in chronic glomerulonephritis

Functional kidney indeces	Normal indices	Dynamics of indices changing					
		Before treatment		On the 5 th day of treatment		On the 10 th day of treatment	
		Control grour	Basic group	Control grour	Basic group	Control grour	Basic group
Blood ammonia, mkmol/l	17. 2 ± 1.12	40.9 ± 1.36	41.3 ± 1.47	36.5 ± 1.87	29.6 ± 1.34	24.4 ± 0.96	16.5 ± 0.61
Blood urea, mmol/l	6. 2 ± 0.72	16.2 ± 0.97	16.9 ± 0.99	14.3 ± 0.98	12.4 ± 0.95	10.6 ± 0.86	7.5 ± 0.56
Blood creatinine, mkmol/l	78.4 ± 2.18	185.9 ± 7.6	198.0 ± 8.7	156.5 ± 8.3	129.0 ± 9.6	129.0 ± 9.6	101.1 ± 2.43
Urine creatinine, mmol/l	4.65 ± 0.17	2.56 ± 0.097	2.79 ± 0.10	2.67 ± 0.11	3.03 ± 0.12	2.89 ± 0.11	4.50 ± 0.17
Filtration clearence at endogen creatinine, ml/min	157.17± 6.28	12.12 ± 0.53	13.24 ± 0.47	14.67 ± 0.67	46,74 ± 1.47	19.94 ± 0.81	112.17 ± 3.87
Meanmolecular blood peptides, mmol/l	0.29 ± 0.001	1.16 ± 0.03	1.22 ± 0.04	1.01 ± 0.036	0.90 ± 0.03	0.90 ± 0.026	0.55 ± 0.032
Meanmolecular urine peptides, mmol/l	0.81 ± 0.03	0.42 ± 0.09	0.44 ± 0.02	0.52 ± 0.02	0.61 ± 0.04	0.65 ± 0.02	0.97 ± 0.03
Minute diuresis, ml/min	2.65 ± 0.06	0.88 ± 0.02	0.94 ± 0.012	0.86 ± 0.02	1.99 ± 0.99	0.89 ± 0.022	2.52 ± 0.24
Glomerular filtration, ml/hour	98.2 ± 2.15	22.4 ± 1.03	21.8 ± 1.06	28.9 ± 2.7	66.5 ± 3.6	35.3 ± 1.96	81.9 ± 2.06
Canal reabsobtion, %	97.4 ± 3.18	95.7 ± 2.18	96.3 ± 2.29	95.6 ± 2.19	95.4 ± 2.21	95.9 ± 2.18	96.5 ± 1.96

Note: The control group was given Lespenephril orally in dose 0.7 ml/kg of the 3 times a day, for 10 conseguent days. The basic group was given the offered substance intravenously, once a day, during 10 days, in dose 10 mg day

Table 3

Influence of the unitary parenteral injection of the offered compound on the blood glucose level in rats with experimental hyperglycaemia

Periods of blood glucose testing	Glucose consentration in blood, mmol/l		
	Control	Substance, 5 mg/kg	Substance, 10 mg/kg
Number of animals	24	24	24
Intact animals index	5.37 ± 0.27	5.62 ± 0.43	5.71 ± 0.45
On the expiration of 30 min atter the inital injection of the compound to the animals with hyperglycaemia	6.85 ± 0.35	4.86 ± 0.53	4.20 ± 0.37
On the expiration of 60 min atter the inital injection of the compound to the animals with hyperglycaemia	7.45 ± 0.50	4.55 ± 0.25	4.01 ± 0.28
On the expiration of 90 min atter the inital injection of the compound to the animals with hyperglycaemia	6.50 ± 0.35	4.93 ± 0.45	4.38 ± 0.35
On the expiration of 120 min atter the inital injection of the compound to the animals with hyperglycaemia	5.55 ± 0.30	5.72 ± 0.53	5.61± 0.50

Hypoglycaemic effect of the offered substance was also studied on the model of alloxan diabetes.

In this series of experiment were used 28 white male rats. Experimental diabetes in comparatively light form (animals with mean hyperglycaemic indices 13.8 ± 2.1 mmol/l - first group) and more complicated forms (animals with mean glycaemic indices 22.3 ± 2.4 mmol/l - the second group) was reproduced by subcontanious injection of alloxan (tabl. 4).

Taking into account the fact, that the offered substance in the case when hyperglycaemia was induced by glucose solution produced more effect being injected in a dose 10 mg/kg, in the given series of the experiment antidiabetic effect of this dose was studied.

The animals of the both groups were intravenously injected the substance daily during 5 days. Blood for the analysis was taken on the fifth day of treatment and in five days after the termination of the treament. The received results are generalized in Table 4.

As it is seen from the data shown in table 4 medical effect of the substance is displayed in the animals both with with light, and with complicated form of diabetes. It is necessary to note the fact, that hyperglycaemic effect produced by the offered substance on the blood glucose level is characterized by equal final indices and doesn't mostly

depend on the condition of the patient in the incipient diabetes.

The analysis of the received results allows us to conclude, that the substance being parenterally injected is potentially effective blood glucose reducing preparation in treating diabetes induced by pancreas disfunction

Table 4

Influence of the compound on the blood glucose level in rats with alloxan disbetes

Periods of blood glucose testing	Glucose consentration in blood, mmol/l	
	Control group	Experimental group
Intact animals index	5.8 ± 0.62	
The first group of animals		
On the expiration of 1 day after the injection of alloxan	13.8 ± 2.1	13.8 ± 2.1
On the 5 th day of treatment	12.3 ± 1.9	9.6 ± 1.3
On the expiration of 5 days after treatment	8.5 ± 0.85	6.8 ± 0.55
The second group of animals		
On the expiration of 1 day after the injection of alloxan	22.3 ± 2.4	22.3 ± 2.4
On the 5 th day of treatment	20.1 ± 1.9	16.9 ± 2.3
On the expiration of 5 days after treatment	18.5 ± 2.0	9.1 ± 0.91

Comparative influence of the offered substance, maniil and diabeton taken orally, on the blood glucose level was studied.

In this series of experiment were used 30 white rats of both gender with weight of a body 165 - 180 g. Experimental diabetes was reproduced by subcontanious injection of alloxan in a dose 150 mg/kg.

The animals with alloxan diabetes were divided(shared) into four groups:

The first group received the offered substance orally in a dose 10 mg/kg once a day during 10 days.

The animals of the second group were given maninil (manufactured by the firm Berlinchemy, Germany) orally in a dose 5mg/kg daily during 10 days.

The third group of the animals recieved diabeton (manufactured by the firm Servie, France) orally during 10 days in a dose 75 mg/kg with the same frequency, as the animals of the previous groups

The fourth group was considered control and those animal were injected saline solution during 10 days .

Blood glucose of the animals was tested before the injection of alloxan, on the day of injection, on the 10 day after injection of alloxan, after treatment with preparations, on the 20 th day of the observation of the animals, i.e. on the expiration of 10 days after the final injection of the preparations.

The results of the conducted research are shown in table 5.

Table 5

Influence of the offered compound, maninil and diabeton on the blood glucose level in the animals with alloxan diabetes

Time of blood glucose testing	Glucose concentration in blood, mmol/l			
	Control	Substans	Maninil	Diabeton
Intact animals index	5.6 ± 0.59			
Index of the animals with alloxan diabetes	17.58 ± 2.25			
Number of animals	6	8	8	8
Index on the expiration of the 10 day after the initial injection of the compound	6.1 ± 2.06	11.95 ± 1.9	2.46 ± 1.93	2.72 ± 2.3
Index on the expiration of the 10 th day after final injection of the compound	4.8 ± 1.05	10.30 ± 1.6	1.36 ± 1.57	0.78 ± 1.7

The conducted research has shown, that during the experiment all the studied preparations have obvious hypoglycaemic effect. And the offered substance concerning its hypoglycaemic effect is not less effective than the known preparations maniil and diabeton. So, if maninil on the 10 th day of treatment has lowered the level of blood glucose by 29.2 %, i.e. from 17.58 ± 2.25 mmol/l to 12.46 ±1.93 mmol/l, and diabeton has lowered concentration of blood glucose by 27.6 %.i.e. to 12.72 ± 2.3 mmol/l. Under the influence of the offerd substance blood glucose level has decreased by 32 % and has made 11.95 ± 1.9 mmol/l. It is necessary to note , that the blood glucose level in the control group remained rather high.

The comparative analysis of hypoglycaemic efficiency of the offered and known substances - bis - (+,– - methionine - picolinate) zinc tetrahydrate in alloxan diabetes are shown in table 6.

As it is seen from the data, shown in tab. 6 the offered substance being taken orally in a shorter period of treatment produces an equivalent hyperglycaemic effect in comparison with the known compound. At the same time the offered substance being taken parenterally much surpasses hyperglycaemic indices of the known preparations in 5 days.

Table 6

Influence of the known and offered compound on the blood glucose level in animals with alloxane diabetes

Substance	Metod and periods of injections	Blood glucose level after diabetes reproduction	Blood glucose level after treatment	Blood glucose reduction of index in comparison to the initial level (100%)
Bis - (+, - - methionine-picolinato) zinc	Paranteraliy, 15 days	209 ± 18, mg%	120 ± 15, mg%	57.42
The offered preparation	Orally, 10 days	17.58 ± 2.25, mmol/l	10.3 ± 1.60, mmol/l	58.59
	Paranteraliy, 5 days	22.3 ± 2.40, mmol/l	9.1 ± 0.91, mmol/l	40.81

Influence of the preparation on glucose transport was studied on cell culture of rats. Isolated from the muscles of the back rat paws by the method of Wallberg – Henriksson. Received data are shown in table 7.

Table 7

Influence of the offered compound on glucose transport through the membrane (intracellular concentration of glucose in skeleton muscles)

Conditions of the experiment	Intracellular glucose concentration	
	in units	in %
Control	63.5 ± 3.50	100.00
Insulin, 0.1 IU / g. of tissue	152.4 ± 4.7	240.00
Offered compound, 5 mk g / g. of tissue	114.9 ± 1.0	180.94
Offered compound, 10 mk g / g. of tissue	117.1 ± 5.5	184.41

As it is it seen from the data, one of the possible mechanisms of hypoglycaemic action of the offered substance is, as well as in case of the known hypoglycaemic preparations, increasing intercellular glucose localization.

In experiment conducted on 14 rats of both genders with the weight of a body 140 - 160 g the influence of the offered substance on urination according to the standard technique was studied.

Control experiment was conducted with waterloading. For this purpose each animal was infused 4 ml of distilled water on 100 g of live weight. After water loading the animals were located in exchange chambers for 24 hours for the measurement of initial amounts of excreted urine. After 3 control measurements of volume of excreted urine the

animals were divided into 2 groups:

The first group was considered control (6 animals). The animals of this group were intravenously injected with water for injections in volume 0.3 ml on 100 g of live weight;

The second group was experimental (8 animals) and the animals of this group intravenously received the offered substance in a dose 10 mg/kg unitary. And, this amount of the preparation was infused in volume of injectional liquid in dose of 0.3 ml on 100 g of live weight.

The received data are shown in table 8.

Table 8

Influence of the unitary injection of the offered compound in dose 10 mg/kg on rat diures

Groups of animals	Average amount of urine excretered per day, normal, ml	Average amount of urine, excretered fora day under water load, ml	Difference between indices of urination, normal and after water load, ml
Контрольная	5.4 ± 0.7	6.0 ± 1.2	0.6
Опытная	5.2 ± 0.7	7.7 ± 1.0	2.5

During the conducted research it was found out, that the substance in the studied dose raisees urination by 47.9 % in comparison with initial indices (this index for the control group makes 11.11 %) and 4.16 times, or 416.67 % ,exceeds indices of control group of the animals after water loading.

The formula of the Invention

1. Coordination compound manganase with glutamic acid and vitamin C of the formula $C_{11}H_{15}MnO_{10}N \cdot nH_2O$, where n = 1 - 3, having medical effect in kidney disease treating .hypoglycaemic and diuretic effect

2. The mode of production of the coordination compound manganase with glutamic acid and vitamin C is peculiar because the specified coordination compound is received by interaction of salt manganase with glutamic acid and vitamin C at molar ratio salt manganase : bi substituted salt of glutamic acid : vitamin C equal 1 : 1 : 1

3. The mode of production coincides with thet described in point 2 b u t bi-substituted salt of glutamic acid interacts with manganase salt at equimolar ratio in water medium, and the purified product is added to water solution of vitamin C in equimolar quantity

4. The mode of production coincides with that described in b u t in water medium natrium intercts potassium hydroxide : glutamic acid : manganase salt : vitamin C molar ration equal 2 : 1 : 1 : 1

5. Pharmaceutical compound, producid medical effect in kidney disease treament, hypoglycaemic and diuretic action, containind active substance and pharmaceutically acceptable additional substances or dissolvent differs in the fact that as active substance it contains the compound with general formula $C_{11}H_{15}MnO_{10}N \cdot nH_2O$, where n = 1 - 3, amounted 0.001 - 1.0 g as daily dosage

6. Pharmaceutical compound coincides with that discribed in point 5, b u t it is applied for effective removal of uremic toxines; for increasing of glomerular filtration and minute diuresis in treatment of acute ant chronical forms of kidney disease

7. Pharmaceutical compound coincides with that discribed in point 5, b u t it is applied for effective reduction of blood glucose level in treatment of acute and chronical forms of hyperglycaemia

INTERNATIONAL SEARCH REPORT

Inte... nal Appl... ...
PCT/UZ 99/00001

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K33/32 A61P13/12 A61K31/375

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 33877 A (NEUMANN WILLIAM L ;HENKE SUSAN L (US); MONSANTO CO (US); WEISS RAN) 18 September 1997 (1997-09-18) *cf. abstract, page 3, lines 19-24, page 8, lines 13-18, claim 18*	1-7
A	WO 98 16218 A (PHILLIPS ROSEMARY HELEN ;CORTECS UK LTD (GB); CHEVALIER SYLVAINE F) 23 April 1998 (1998-04-23) *cf. abstract, page 3,lines 14-24, page 4, lines 9-11*	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2000	23/02/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Stoltner, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern nal Application No
PCT/UZ 99/00001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9733877 A	18-09-1997	AU 1962497 A	01-10-1997
		CA 2249011 A	18-09-1997
		CN 1225631 A	11-08-1999
		CZ 9802711 A	13-01-1999
		EP 0891338 A	20-01-1999
		NO 984164 A	06-11-1998
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WO 9816218 A	23-04-1998	AU 4631697 A	11-05-1998
		EP 0942720 A	22-09-1999

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L22: Entry 1 of 1 File: DWPI Sep 21, 2000

DERWENT-ACC-NO: 2000-594407
DERWENT-WEEK: 200056

TITLE: New coordination compound comprising manganese, glutamic acid and vitamin C, with hypoglycemic and diuretic activity, useful for treating kidney disease and diabetes

INVENTOR: AKBAROV, A B; ARIPKHODZHAEVA, F A

PATENT-ASSIGNEE:

ASSIGNEE	CODE
AKBAROV A B	AKBAI

PRIORITY-DATA: 1999UZ-0000160 (March 15, 1999)

Search Selected | Search ALL | Clear

PATENT-FAMILY:

	PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
☐	WO 200054784 A1	September 21, 2000	E	017	A61K033/32

DESIGNATED-STATES: IN US UZ AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 200054784A1	March 16, 1999	1999WO-UZ00001	

INT-CL (IPC): A61 K 31/375; A61 K 33/32; A61 P 13/12

ABSTRACTED-PUB-NO: WO 200054784A

BASIC-ABSTRACT:

NOVELTY - A new coordination complex comprising manganese, glutamic acid and vitamin C has both hypoglycemic and diuretic activity, and is useful for treating kidney disease and diabetes.

DETAILED DESCRIPTION - A coordination compound comprising manganese, glutamic acid and vitamin C, of formula C11H15MnO10N.nH2O (I) (n = 1-3) is new.

An INDEPENDENT CLAIM is included for the preparation of (I).

ACTIVITY - Hypoglycemic; diuretic.

h e b b g e e e f c e e ge

Acute renal failure was produced in rats by intramuscular injection of 50% aqueous glycerine (10 mg/kg). After 24 hours, one group (A) was injected with (I) (10 mg/kg) for 10 days, while the control group (B) received water for injection. Tests were carried out on urine and blood, e.g. blood levels of ammonia on days 1 and 10 for (A) and (B) were 37.90 plus or minus 1.22 and 16.3 plus or minus 0.52 mmol/l, and 41.6 plus or minus 1.58 and 39.61 plus or minus 1.09 mmol/l respectively; compared with 17.9 plus or minus 1.34 mmol/l for an intact, untreated control group.

The volume of urine excreted during the first 24 hours after dosing was 5.23 plus or minus 0.78 ml for group (A) compared with 2.43 plus or minus 0.70 ml for (B), and on day 10 the diuresis index was 2.5 times higher for (A) than (B). For an intact, untreated group, the volume of urine was 4.21 plus or minus 0.59 ml/day.

MECHANISM OF ACTION - None given.

USE - For treating kidney disease, e.g. for removal of uremic toxins, for increasing glomerular filtration and minute diuresis in treatment of acute and chronic forms of kidney disease; and for reduction of blood glucose level in treatment of acute and chronic hyperglycemia, also diabetes connected with pancreas dysfunction.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: NEW COORDINATE COMPOUND COMPRISE MANGANESE GLUTAMIC ACID VITAMIN DIURETIC ACTIVE USEFUL TREAT KIDNEY DISEASE DIABETES

DERWENT-CLASS: B05

CPI-CODES: B03-F; B05-A03A; B10-B02E; B14-N10; B14-N13; B14-S04;

CHEMICAL-CODES:

Chemical Indexing M2 *01*
Fragmentation Code
A425 A950 A960 C108 C550 C710 C801 C802 C803 C804
C805 C807 F012 F013 F014 F015 F017 F113 H100 H181
H404 H422 H482 J012 J172 J521 L942 M280 M312 M313
M321 M332 M343 M349 M373 M381 M391 M411 M510 M520
M521 M530 M540 M630 M710 M720 M800 M904 M905 N104
N422 N513 N514 P722 P723 P816
Specfic Compounds
A2IP6T A2IP6N A2IP6P

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C2000-177568